

REMARKS

Claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46-47 and 50-51 are currently pending.

RESTRICTION REQUIREMENT

Applicants elected the invention of Group I, namely, claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46-47 and 50-51.

THE CLAIMED INVENTION

The invention is directed to novel methods that replenish glutathione (GSH) using sulfhydryl protected glutathione prodrugs. Before Applicants' invention, no one taught or suggested using sulfhydryl protected glutathione prodrugs to replenish GSH in a subject.

REJECTION UNDER 35 U.S.C. §103(a)

The Examiner rejected claims 1-4, 7, 9-10, 20-22, 25-26, 33-35, 38-39, 46-47 and 50-51 as unpatentable over Demopoulos et al., U.S. Patent 6,159,500 and Eriksson et al. for reasons of record.

Applicants respectfully disagree.

A. THE LEGAL STANDARD FOR ESTABLISHING OBVIOUSNESS UNDER 35 U.S.C. §103

The legal standard for a rejection under §103 is as follows. As set forth in MPEP §2143:

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicants' disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 148 USPQ 459, 467 (1966). To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the Applicants' achievement, that must establish the obviousness of the combination.

The teachings of the references, their relatedness to the field of the Applicants' endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. See *In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). When the references are in the same field as that of

the Applicants' invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the Applicants, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

B. APPLICANTS HAVE MET THE LEGAL STANDARD FOR NONOBVIOUSNESS

Applicants have met the legal standard for nonobviousness because none of the cited references suggest the use of sulfhydryl protected glutathione prodrugs to replenish GSH in a subject as claimed.

U.S. Patent 6,159,500 by Demoupolos et al.

The '500 patent teaches only a formulation of GSH with ascorbic acid ('500 patent at col. 8, lines 15-33). Further, the '500 patent reiterates what is generally well known, namely, that oxidative stress causes GSH depletion in cells/organs, and repletion of GSH, by supplying GSH, either by their biochemical precursors or with GSH itself should alleviate the condition.

Throughout, the '500 patent emphasizes that GSH itself must be administered together with ascorbic acid (their formulation), to reduce the static charge of dry GSH and for "maintaining glutathione in a reduced state".

The '500 patent does not suggest that GSH can be replenished by administering to a subject a GSH ester, and certainly NOT a sulfhydryl protected glutathione prodrug such as GSSG or CySSG as claimed. In fact, since GSH is not orally bioavailable in a subject

to any extent, for bioavailability, the '500 patent requires the addition of ascorbic acid with the GSH in their formulation.

Further, the '500 patent teaches that glutathione esters are more expensive than glutathione itself and have proven toxic ('500 patent at col. 2, lines 48-52). Therefore, the '500 patent "teaches away" from using glutathione esters for administration as bioavailable sources of glutathione.

Nowhere does the '500 patent suggest sulfhydryl protected glutathione prodrugs to replenish GSH in a subject as claimed. This deficiency is not remedied by Eriksson et al.

Eriksson, Stellan A. and Bengt Mannervik, "The Reduction of the L-cystein-glutathione mixed disulfide in Rat Liver," FEBS Letters, March 1970, 742:26-28

Eriksson teaches that CySSG is in equilibrium with GSSG.

However, Eriksson does not suggest that one could use sulfhydryl protected glutathione prodrugs to replenish GSH.

The Examiner states that it would have been obvious to use any of GSH and GSH's precursors, namely, CySH, GSH, GSSG or CySSG, to "replenish the intracellular concentration of such an important small molecule". However, Applicants note that that suggestion is not found in the prior art. Moreover, GSH and its precursors are not equivalents. For example, L-Cysteine (L-CySH), which is not a sulfhydryl protected glutathione prodrug, would be readily catabolized in a subject; hence, L-CySH must be administered as one of its prodrug forms (e.g., NAC, OTCA or RibCys)—also none of which are sulfhydryl protected glutathione prodrugs. Further, Figure 1 of the subject application shows that L-CySSG, a sulfhydryl protected glutathione prodrug, is superior to GSH-OEt, a sulfhydryl unprotected glutathione prodrug, to replenish GSH depletion in ACP-induced hepatotoxicity in mice.

Before Applicants' invention, no one suggested the use of exogenously administered GSSG to replenish intracellular GSH, because GSSG is the product of GSH when protecting cells from oxidative stress, and the cited references suggest that it is the reduced form (GSH) that should be given and not the oxidized form (GSSG). Applicants were the first to provide experimental evidence that an exogenously administered sulfhydryl protected glutathione prodrug, e.g., L-CySSG, can protect the liver from the toxic insult of acetaminophen, a drug known to severely deplete GSH and elicit hepatotoxicity.

The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430, cited in MPEP §2143.01. There must be a reason or suggestion in the art for modifying the prior art other than the knowledge learned from applicants' disclosure¹. However, the cited references provide none. The primary reference, the '500 patent, teaches the use of GSH to replenish GSH. Further, the secondary reference, the Eriksson reference, does not teach or suggest what the primary references fail to teach, namely, the use of sulfhydryl protected glutathione prodrugs to replenish GSH as claimed. Further, there would have been no motivation to substitute GSH of the prior art to the sulfhydryl protected glutathione prodrugs of the claimed methods because it was taught that GSH and sulfhydryl protected glutathione prodrugs are not equivalents. Accordingly, the combination of the primary and secondary references does not and cannot render obvious the claimed methods.

CONCLUSION

¹ *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

Applicant: Herbert T. Nagasawa et al.
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If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

No fee, other than the \$120.00 fee for one-month extension of time, is deemed necessary in connection with the filing of this Communication. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,



Sarah B. Adriano
Registration No. 34,470
SaraLynn Mandel
Registration No. 31,853
Mandel & Adriano
55 So. Lake Ave., Suite 710
Pasadena, California 91101
626/395-7801
Customer No: 26,941